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The Neurobehavioral Consequences of Low Lead Exposure in Childhood

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NEEDLEMAN, H. L. *The neurobehavioral consequences of low level lead exposure in childhood.* NEUROBEHAV TOXICOL TERATOL 4(6) 729–732, 1982.—Children attending non-remedial first and second grades were classified according to the concentration of lead in their shed deciduous teeth. Children in the lowest and highest tenth percentile were studied with a detailed neuropsychological battery under blind conditions. Thirty-nine non-lead covariates were controlled either by matching or in the biostatistical analysis. High lead children tended to have significantly lower IQ scores particularly on the verbal scales of the WISC-R, impaired auditory and language processing, increased reaction times at longer intervals of delay. Their teachers who were blind to the dentine lead levels found an increased incidence of disordered classroom behavior in direct relationship to the concentration of lead in their teeth. Quantitative electroencephalographic analysis demonstrated decreased midline alpha and increased midline delta in high lead subjects. Four years later a subsample of these children was followed up and observed during quiet classroom activity. High lead children tended to spend more time off tasks staring at classmates, out the window or at the observer. These observations demonstrate that lead at doses below those which are associated with frank clinical symptoms produce deficits in intelligence, attention, auditory-language function and disordered classroom behavior.

Low level exposure Lead Dentine concentrations Children IQ Attention Auditory-language function Classroom behavior

WHILE experimental studies of lead toxicity in the intact animal and in cellular preparations have been essential in defining dose-effect relationships and in clarifying potential mechanisms of toxicity, the study of human populations is required to set regulatory standards establishing allowable concentrations of pollutants in the biosphere.

In this paper I review a series of studies which have focussed on one question: Does lead at exposures insufficient to yield a clinically diagnosable picture of intoxication in childhood produce measureable neuropsychologic impairment? This question has generated considerable interest and an equal measure of controversy over the past decade [5,8]. Epidemiologic studies of real world populations can by definition never hope to achieve the control of independent and intervening variables towards which experimentalists aspire. Among the reasons for the differences between published conclusions are four methologic issues which have vexed the study of lead at low dose. They are: (1) Poor markers of exposure to lead. Blood lead levels reflect recent exposure only and may misclassify subjects after exposure has ended. (2) Weak markers of outcome. The detection of smaller subtle alterations require sensitive, reliable and appropriately chosen measures of neuropsychologic performance. (3) Lack of control of non-lead covariates which could be confounders. (4) Ascertainment bias. Subjects who enter a study may differ systematically with respect to either independent or outcome variables from those who are excluded.

My colleagues and I set out to measure neuropsychological function in relation to lead exposure while addressing these issues [6].

METHOD

From a population of 3329 children attending ordinary (non-remedial) first and second grades, shed deciduous teeth were collected from 2335 (70%) of the subjects. Teachers were asked to rate children on an eleven-item forced choice questionnaire evaluating classroom behavior after they knew the child for at least two months. Teachers were blind to the child's lead burden.

Teeth were sliced and dentine measured by methods previously described [4]. The distribution of dentine lead levels was log normal with a median of 12 ppm. The 10th percentile was 8.7 ppm and the 90th percentile was 24 ppm. Children in the 10th and 90th percentiles were provisionally selected for detailed neuropsychological evaluation. If the second dentine specimen was concordant with the first, and if the mean of the two samples was either more than 20 ppm or less than 10 ppm, they were included in the study. Parents were contacted by telephone, and the child invited into the study if English was the first language spoken at home, if the child was born at-term, had never had lead toxicity or a noteworthy head injury. Comparisons of included and excluded subjects on teacher's rating and on distributions of dentine lead levels were made and revealed no bias along either dimension.

Mothers came to the neuropsychological laboratory and completed a lengthy questionnaire evaluating 39 non-lead covariates including a brief IQ test. Children received a comprehensive test battery administered in fixed order by two trained examiners blind to the child's lead level [6].

TABLE 1

COVARIATES WHICH DIFFERED AT $p<0.1$, AND WHICH WERE CONTROLLED IN THE ANALYSIS

	Low Lead	High Lead	p Value
Mother's age at subject's birth (year)	26.2 ± 5.5	24.5 ± 5.8	0.07
Mother's education (grade)	11.9 ± 2.0	11.4 ± 1.7	0.08
Father's social class (2 factor Hollingshead)	3.8 ± 1.0	4.1 ± 0.8	0.02
Number of pregnancies	3.3 ± 1.8	3.8 ± 2.3	0.10
Parent IQ	111.8 ± 14.0	108.7 ± 14.5	NS

COVARIATES WHICH DID NOT DIFFER AT $p<0.1$

Marital status of parents
Height, weight, head circumference
Birth weight
Length of hospital stay after birth
Number of admissions to hospital

TABLE 2

OUTCOMES WHICH DIFFERED BETWEEN HIGH AND LOW LEAD GROUPS AT $p<0.05$

		Low Lead mean	High Lead mean	p Value* (2 tail)
WISC-›	WISC-R			
Full ?	Full Scale IQ	106.6	102.1	0.03
Verba	Verbal IQ	103.9	99.3	0.03
Perfo:	Performance IQ	108.7	104.9	0.08
Seashor	Seashore Rhythm Test			
Subte:	Subtest A	8.2	7.1	0.002
Subte:	Subtest B	7.5	6.8	0.03
Subte:	Subtest C	6.0	5.4	0.07
Sum	Sum	21.6	19.4	0.002
Token T·	Token Test			
Block	Block 1	2.9	2.8	0.37
Block	Block 2	3.7	3.7	0.90
Block	Block 3	4.1	4.0	0.42
Block	Block 4	14.1	13.1	0.05
Sum	Sum	24.8	23.6	0.09
Sentence	Sentence Repetition Test	12.6	11.3	0.04
Reaction Varying I Delay	Reaction Time Under Varying Intervals of Delay	(mean±S.D.)	(mean±S.D.)	
Block 1	Block 1 (3 sec)	0.35 ± 0.08 sec	0.37 ± 0.09 sec	0.32
Block 2	Block 2 (12 sec)	0.41 ± 0.09	0.47 ± 0.12	0.001
Block 3	Block 3 (12 sec)	0.41 ± 0.09	0.48 ± 0.11	0.001
Block 4	Block 4 (3 sec)	0.38 ± 0.10	0.41 ± 0.12	0.01

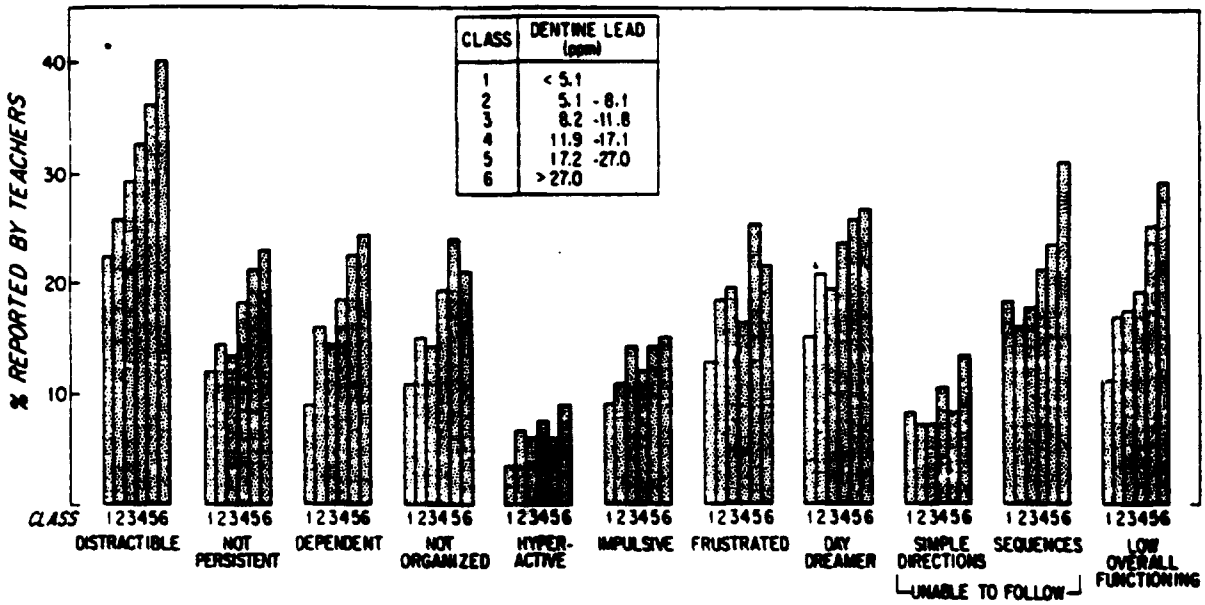

FIG. 1. Distribution of negative ratings by teachers on eleven classroom behaviors in relation to dentine lead concentration. (Reprinted with permission from [6], p. 687.

RESULTS

Of 39 control variables, high and low lead subjects did not differ on 34. The five variables which did differ at $p<0.1$ (Table 1) controlled in an analysis of covariance with lead as the main effect. When this was done high lead subjects were found to be significantly inferior to their low lead controls on a number of outcomes (Table 2). In addition, the portion of negative teacher's ratings increased with dentine lead concentrations across the entire range of lead levels (Fig. 1).

DISCUSSION

In this study a direct attempt was made to address the four major design issues. Dentine lead levels are a permanent record of past exposure. The sample was an unbiased representation of the population with regard to lead and classroom behavior; 39 non-lead covariates were controlled; and a panel of sensitive instruments were employed one child at a time by trained examiners.

We conclude that lead at doses below which bring children to medical attention is associated with significant differences of psychometric intelligence, auditory and language processing and attention. Disordered classroom behavior as evaluated by teachers appears to increase in direct relationship to dentine lead level with no evidence of a threshold detected.

The difference in mean IQ scores of four points reflects a large difference in the extremes. When the cumulative frequency distribution of verbal IQ's plotted and the relative proportion of subjects with IQ's below 80 measured, it is seen that high lead subjects have an almost four-fold increase in the proportion of subjects scoring at the low end. In addition, 5% of the low lead subjects were over 125. No high lead subjects exceed this figure (Fig. 2). The incidence of pica is almost three times as high in the high lead group, leading some to suggest that lead burden is a dependent variable secondary to disordered CNS function as expressed by pica. Adjustment for the potential confounding effect of pica on verbal IQ scores [7] revealed no change in the relative risk of low IQ after adjustment.

Burchfiel *et al.* [2] studied a subsample of these subjects using quantitative electroencephalograms and found that high lead subjects had significantly less midline alpha and more midline delta. When EEG power spectra data was added to the neuropsychologic outcomes studied in this sample and a stepwise discriminant function analysis applied, the separation between high and low lead groups increased dramatically. Bellinger *et al.* [1] studied a subsample of the same group of children four years later in a classroom setting. The observers, blind to the earlier lead burden, counted on and off task behaviors of the children at seven second intervals over four 3-minute pochs. High lead children were found to spend significantly more time off task, staring out the window at their peers or at the observer than their low lead control.

The inferences drawn in the studies reported here have received support from two other groups of investigators. Yule and colleagues [10] classified London children according to blood lead levels and found dose dependent differences in IQ, reading, and spelling. In a more recent report, the same group [3] employing the same teacher's rating scale using in the American studies, found strikingly similar changes. Winneke and colleagues [9] studied children in two towns, classifying their lead exposure by tooth lead levels. In their first study they found that children from Duisburg with larger amounts of lead in their teeth were inferior on two measures of perceptual-motor integration and on IQ. In a later study conducted on Dusseldorf children (this volume), similar effects were found. In the latter study, higher lead subjects were inferior on a reaction time performance, on a measure of perceptual motor performance, and were rated as more restless and distractible by their mothers. Intelligence test scores did not differ after controlling for "socioheriditary background." This was scaled by a two-factor score

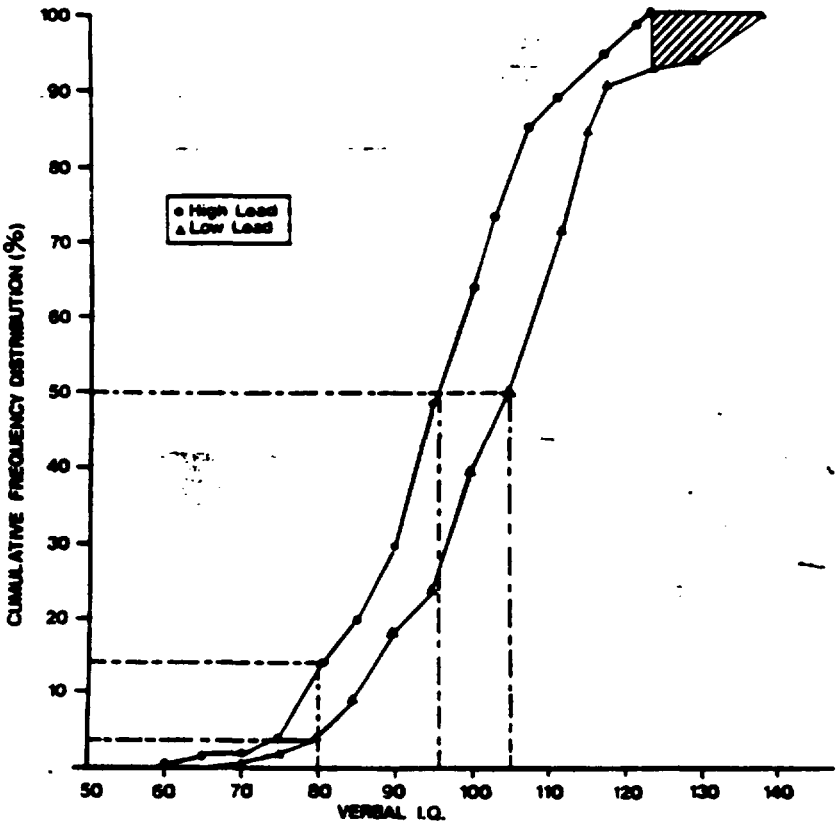

FIG. 2. Cumulative frequency distributions of verbal IQ scores in high and low lead subjects. (Reprinted with permission from [7].)

consisting of father's occupation and type of school placement. Since school placement was done on recommendation of the teacher, it is likely that this was determined by the student's IQ and class performance. This may well be a case in which an outcome variable (school performance) is controlled, leading to obscuring of a truly positive effect of lead on IQ. Examination of Winneke's data without controlling for type of school may permit evaluation of this possibility.

Conclusions

Lead at low doses, which does not produce a syndrome clear enough to warrant medical attention, is associated with a number of neuropsychological deficits. These include diminished language function and auditory processing, and altered electroencephalographic patterns. These changes appear to be enduring and to be manifest in altered classroom performance when students are followed up four years later.

ACKNOWLEDGEMENTS

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